1 526 410

PATENT SPECIFICATION

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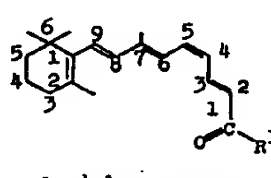
(54) 4-(E)- AND 4-(Z)-7-METHYL-9-(2,6,6-TRIMETHYL-1-CYCLOHEXEN-1-YL)-NONA-2,4,6,8-TETRAENECARBOXYLIC ACID, THEIR DERIVATIVES AND PREPARATIONS CONTAINING SAME

(71) We, BASF AKTIENGESELLSCHAFT, a German Joint Stock Company of 6700 Ludwigshafen, Federal Republic of Germany, do hereby declare the invention, for which we pray that a Patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following Statement:—

The present invention relates to pharmacologically active 4 - (E) - and 4 - (Z) - 7 - methyl - 9 - (2,6,6 - trimethyl - 1 - cyclohexen - 1 - yl) - nona - 2,4,6,8 - tetraenecarboxylic acid, their derivatives, a process for their manufacture and the preparations in which they are present. These compounds will be referred to below as 11 - cis - 13 - desmethyl - vitamin - A - acid, and as derivatives of 11 - cis - 13 - desmethyl - vitamin - A - acid, respectively.

According to the invention, there is provided a compound which is an 11 - cis - 13 - desmethyl - vitamin - A - acid or a derivative thereof which has the general formula I, below:—



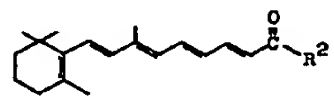
I

where R^1 is hydroxy, alkoxy of 1 to 4 carbon atoms, phenoxy which is unsubstituted or substituted by hydroxyl or carboxyl, amino which is unsubstituted, or monosubstituted or disubstituted by alkyl of 1 to 4 carbon atoms or by phenyl which is unsubstituted, or substituted by hydroxyl, alkyl of 1 to 4 carbon atoms, carboxyl, carboxymethyl or carboxyethyl, a saturated nitrogen-containing heterocyclic ring of 3 to 6 members, which may or may not contain oxygen as a ring member, acyl of 2 to 4 carbon atoms, azido, hydrazino which is unsubstituted or substituted by methyl or phenyl, or $C_{18}H_{25}CO—O—$ having the configuration of 11-cis-13-desmethyl-vitamin-A-acid.

R^1 may be, for example, one of the following: alkoxy of 1 to 4 carbon atoms, eg. methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec.-butoxy and tert.-butoxy, but especially ethoxy and isopropoxy, the latter being particularly preferred: phenoxy, which may be unsubstituted or substituted by hydroxyl or carboxyl, eg. phenoxy and 2-carboxyphenoxy, the latter being particularly preferred; amino groups which may be unsubstituted or monosubstituted or disubstituted and where the substituents are alkyl of 1 to 4 carbon atoms or phenyl which may in turn be substituted by hydroxyl, alkyl of 1 to 4 carbon atoms, carboxyl, carboxymethyl or carboxyethyl, eg. amino, methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, sec.-butylamino, tert.-butylamino, iso-butylamino, phenylamino, 3,4-dimethylamino, 4-carboxyphenylamino, 4-carboxymethylphenylamino, 4-carboxyethylphenylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino and diphenylamino, 3,4-dimethylamino and 4-carboxyethylphenylamino being particularly preferred; saturated nitrogen-containing heterocyclic rings of 3 to 6 members which may or may not contain oxygen as a ring member, eg. the aziridine, piperidine or morpholine radical, amongst which the piperidine and morpholine radicals are particularly preferred: acyl of 2 to 4 carbon atoms, eg. acetyl, propionyl and butyryl; hydrazino which may or may not be substituted, eg. hydrazino, methylhydrazino or

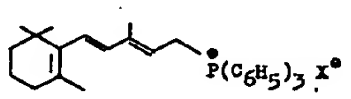
phenylhydrazino. R^1 may furthermore be $C_{18}H_{25}CO—O—$ having the configuration of 11-cis-desmethyl-vitamin-A-acid.

The invention also provides pharmaceutical preparations which contain one or more compounds as just defined, the preparation also containing one or more conventional carriers and/or one or more conventional diluents. Such preparations may contain as a further active ingredient an all-trans-13-desmethyl-vitamin-A-acid or a derivative thereof. Such all-trans acid or derivative has the general formula:—



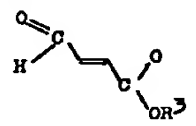
in which R^2 is alkoxy or 2 to 4 carbon atoms, eg. ethoxy, n-propoxy, isopropoxy, n-butoxy, sec.-butoxy, tert.-butoxy and isobutoxy, isopropoxy being particularly preferred; phenoxy, which may or may not be substituted by hydroxyl or carboxyl, eg. phenoxy and 2-carboxyphenoxy, the latter being particularly preferred; amino groups which may be unsubstituted or monosubstituted or disubstituted and where the substituents are alkyl of 1 to 4 carbon atoms or phenyl which may in turn be substituted by hydroxyl, alkyl of 1 to 4 carbon atoms, carboxyl, carboxymethyl or carboxyethyl, eg. amino, methylamino, ethylamino, isopropylamino, n-butylamino, sec.-butylamino, tert.-butylamino, isobutylamino, phenylamino, 3,4-dimethylamino, 4-carboxyphenylamino, 4-carboxymethylphenylamino, 4-carboxyethylphenylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino and diphenylamino, 3,4-dimethylamino and 4-carboxyethylphenylamino being particularly preferred; saturated nitrogen-containing heterocyclic rings of 3 to 6 members which may or may not contain oxygen as a ring member, eg. the aziridine, piperidine or morpholine radical, amongst which the piperidine and morpholine radicals are particularly preferred; acyl of 2 to 4 carbon atoms, eg. acetyl, propionyl and butyryl; azido; hydrazino which may or may not be substituted by methyl or phenyl, eg. hydrazino, methylhydrazino or phenylhydrazino. R^2 may furthermore be $C_{18}H_{25}—CO—O—$ having the configuration of all-trans-13-desmethyl-vitamin-A-acid.

The invention also relates to a process for the manufacture of 11-cis-13-desmethyl-vitamin-A-acid and its derivatives of the formula I as defined earlier, which process comprises reacting a compound of the Formula II below:—



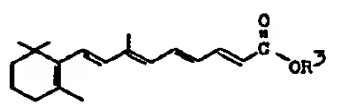
II

where $X^{\ominus}$ is an organic or inorganic acid radical, eg. halide, especially bromide or chloride, bisulfate or tosylate, with a compound of the formula III below:—

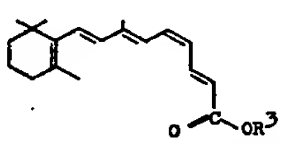


III

where R^3 is hydrogen, alkyl of 1 to 4 carbon atoms (eg. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or sec.-butyl), or an alkali metal ion, eg. sodium or potassium, or ammonium, in an inert solvent, at from −20 to +30°C, in the presence of a base, and separating the resulting isomer mixture of compounds of the formulae IV and V



IV



V

where R^3 has the above meaning, and thereafter effecting a step as specified below:—

(i) recovering the isomer mixture as product,
(ii) recovering from the isomer mixture referred to in (i) a cis-compound as product,

(iii) treating the isomer mixture referred to in (i) or the cis-compound recovered in step (ii) to effect conversion thereof to acid form when said isomer mixture or said cis-compound is in other than an acid or to effect conversion thereof to non-acid form when said isomer mixture or said cis-compound is in acid form,

(iv) treating an isomer mixture formed by conversion as specified in (iii) to recover therefrom a cis-compound,

(v) treating a cis-compound recovered in step (iv) to effect conversion thereof to an acid when said cis-compound is other than an acid or to effect conversion thereof to non-acid form when said cis-compound is an acid.

The starting compounds of the formula II are known and their manufacture may readily be found disclosed in the literature (German Patent 1,060,386).

The manufacture of the fumaraldehyde-acid, or its derivatives or salts (formula III), which are used as starting compounds, is described in Annalen der Chemie, *697* (1966), 42. Preferred starting compounds of the formula III are those where R^3 is hydrogen, methyl, ethyl, sodium, potassium or ammonium.

Suitable inert organic solvents for the reaction of a compound of the formula II with a compound of the formula III in the stated temperature range of from −20 to +30°C are dialkyl ethers and saturated cyclic ethers, eg. diethyl ether, dioxane and tetrahydrofuran, cyclic hydrocarbons, eg. cyclohexane, aromatic hydrocarbons, eg. benzene, toluene, xylene and nitrobenzene, nitriles and esters of lower aliphatic carboxylic acids, eg. acetonitrile and ethyl acetate, acid amides of lower aliphatic carboxylic acids, eg. dimethylformamide, and lower aliphatic alcohols, eg. methanol, ethanol and isopropanol.

Bases which may be used include alkali metal hydroxides, alkaline earth metal hydroxides, alcoholates, eg. sodium methylate and sodium ethylate, amines or (other) nitrogen-containing bases, eg. ammonia. The suitable amount of base to be used can be calculated from the stoichiometric requirement for converting the compound of the formula II into the corresponding ylid.

The above reaction conditions correspond to those of the conventional Wittig reaction (Organic Reactions, *14* (1965), 270). The isomer mixture produced in this reaction can be separated by recrystallization or by column chromatography. A heptane-isopropanol mixture or methanol may be used for the recrystallization. A silica gel column with petroleum ether or petroleum ether/diethyl ether as the developer may be used for the separation by column chromatography.

It is also possible first saponify the esters obtained, of the formulae IV and V, and to carry out the isomer separation at the carboxylic acid stage.

The esters of the formulae IV and V may be saponified by conventional methods. A suitable method is to heat them with from 1 to 3 moles of a strong base, eg. sodium hydroxide or potassium hydroxide, in a suitable alcohol, eg. ethanol, until they have been saponified quantitatively. The carboxylic acids may be separated by recrystallization from methanol or by column chromatography, as described in the case of the separation of the acids.

The 13-desmethyl-vitamin-A-acid compound of the formula I may be manufactured by converting the free acid obtained into a functional acid derivative, eg. the acid chloride, and reacting this with a compound of the formula R^1H or R^2H appropriate to the above meanings of R^1 and R^2.

The preferred functional 11-cis- or all-trans-13-desmethyl-vitamin-A-acid derivative is the corresponding acid chloride, which can be manufactured by conventional methods, without difficulties, by reaction with an inorganic acid halide, eg. thionyl chloride. The acid chloride is suitably used in the form of a solution in an anhydrous organic solvent. Examples of solvents which may be used are diethyl ether, tetrahydrofuran, benzene or toluene. Suitably, the acid chloride is reacted further immediately after it has been produced.

The corresponding acid chloride is reacted with an alcohol, phenol, primary or secondary amine, acid, azide or hydrazine derivative, depending on the meanings of R^1 and R^2, suitably at from −20 to +50°C. It is advantageous to carry out the reaction with exclusion of oxygen, under an inert gas, eg. under nitrogen, and so as to avoid exposure to strong light.

Suitably, the hydrogen chloride produced by the reaction is neutralized with a stoichiometrically equivalent amount of an HCl acceptor. Tertiary amines, eg. triethylamine or pyridine or—if an amide is to be manufactured—an appropriate excess of the amine to be reacted, may be employed as the HCl acceptor.

As will be appreciated from the foregoing, an isomer mixture (of cis- and all-

trans-compounds) can be obtained as the product of the process described, and such mixture may conveniently be used to produce a pharmaceutical composition as referred to earlier. Alternatively, such composition may be prepared from separately prepared isomers, the all-trans compound being conveniently prepared by a process as already described for preparing cis-compounds.

In addition to the compounds mentioned in the Examples, others which deserve individual mention are 11-cis-13-desmethyl-vitamin-A-acid methyl ester, 11-cis-13-desmethyl-vitamin-A-acid ethyl ester and 11-cis-13-desmethyl-vitamin-A-acid isopropyl ester.

The compounds according to the invention, mentioned in claim 1, as well as all-trans-13-desmethyl-vitamin-A-acid and all-trans-13-desmethyl-vitamin-A-acid methyl ester surprisingly exert an effect on cell regeneration. They activate cell metabolism and promote granulation, so that they may be used as therapeutic agents for topical and systemic application.

By way of example, 11-cis-13-desmethyl-vitamin-A-acid exerts a substantially more powerful effect than the known vitamin-A-acid.

If, eg., vitamin-A-acid or 11 - cis - 13 - desmethyl - vitamin - A - acid or its derivatives, eg. 11 - cis - 13 - desmethyl - vitamin - A - acid salicylic acid ester, or all - trans - 13 - desmethyl - vitamin - A - acid, each dissolved in dimethylsulfoxide, is added to a culture of epidermis cells in vitro, obtbained by treatment of guinea-pig skin with trypsin (0.25%), and the culture is incubated for 1 hour with 2 μ Ci ^{3}H-thymidinemethyl-^{3}H, the stimulating effect on cell growth is clearly recognizable from the DNA-synthesis, as measured from the incorporation of thymidine, using liquid scintillation counting (for method, see E. Christophers, The Journal of Investigative Dermatology, *63*, No. 6, 1974). 11-cis-13-Desmethyl-vitamin-A-acid is found to be outstandingly active. When the latter is used at the rate of 10 μg/ml of cell culture, its stimulating effect is, on average, more than one and a half times as great as that of vitamin-A-acid. Compared to the growth of control cell cultures, vitamin-A-acid increases growth about three-fold, but 11-cis-13-desmethyl-vitamin-A-acid increases growth about five-fold. all - trans - 13 - Desmethyl - vitamin - A - acid and 11 - cis - 13 - desmethyl - vitamin - A - acid salicylic acid ester are also active, but to a lesser extent.

The Table which follows shows the effect of all - trans - 13 - desmethyl - vitamin - A - acid, 11 - cis - 13 - desmethyl - vitamin - A - acid and 11 - cis - 13 - desmethyl - vitamin - A - acid salicylic acid ester, compared to that of vitamin-A-acid, on the DNA synthesis of epidermis cells cultured in vitro.

Incubated substance (10 μg/ml)	Number of experiments 1)	Average DNA synthesis in per cent of the control 2)
Control	3	100
all-trans-13-Desmethyl-vitamin-A-acid	1	130.2
11-cis-13-Desmethyl-vitamin-A-acid	3	552.3
11-cis-13-Desmethyl-vitamin-A-acid salicylic acid ester	1	169.2
Vitamin-A acid	3	391.7

1) Each experimental result is a mean value of 3 results.
2) Measured as cpm/culture of 3_H-Tdr incorporation on incubation for 1—2 hours (1 μCi 3_H-TdR)^H.

The outstanding effect of 11-cis-13-desmethyl-vitamin-A-acid on the growth of epithelial cells can also be demonstrated in vivo. If, using the method of Heite (Arzneimittel-Forschung *23* (1973) 1,342), a tissue defect is created on both ears of a rabbit by punching a circular piece of 6 mm diameter, under narcosis, from all the tissue layers of the ear and additionally damaging the defect zone with X-rays (500 R, 55 KV, tube 1.5 cm, distance from skin 10 cm), and in addition the spontaneous healing of the wound is inhibited by daily application of prednisolone (1 to 2 mg/kg, subcutaneously), the daily local treatment on one side with a gel preparation containing 0.05% of 11-cis-13-desmethyl-vitamin-A-acid or all-trans-13-desmethyl-vitamin-A-acid or vitamin-A-acid leads, in the course of from 4 to 7 weeks, to a significantly more rapid healing of the defect than does a treatment with a blank gel (ie. not containing the active compound) on the contra-lateral side.

Here again, 11-cis-13-desmethyl-vitamin-A-acid exhibits the treatest cell-regenerating activity. Thus, the diameter of the wound was reduced, in the course of 6 weeks, by 54%, based on the size of the defect at the beginning or the test, by 11-cis-13-desmethylvitamin-A-acid, by 43% by vitamin-A-acid and by from 17.2 to 19.9% by a blank gel.

The compounds to be used according to the invention may be employed for treating conditions associated with disturbances in cell regeneration, eg. burns, unsatisfactory healing of wounds, acne, disturbances in cornification, eg. ichthyosis, psoriasis, pityriasis, rosacea or dandruff.

Accordingly, the invention also relates to therapeutic agents which contain one of the compounds of formula I as defined earlier, all-trans-13-desmethyl-vitamin-A-acid or all-trans-13-desmethyl-vitamin-A-acid methyl ester optionally being present as additional active ingredient, together with one or more conventional carriers or diluents.

Depending on the desired type of application, suitable pharmaceutical preparations may be formulated by conventional methods, using conventional pharmaceutical auxiliaries. Preparations for external application to the skin are, eg., solutions, gels, creams, ointments or powders, whilst preparations for systemic use are, eg., tablets, capsules, dragees or solutions.

Very particularly preferred preparations are solutions, creams and gels for local application and drops and capsules for systemic application.

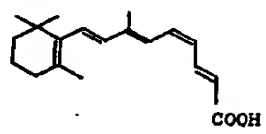
The preferred preparations contain 11-cis-13-desmethyl-vitamin-A-acid or its derivatives, but 11-cis-13-desmethyl-vitamin-A-acid and 11-cis-13-desmethyl-vitamin-A-acid salicylic acid ester should be singled out particularly.

For local application, the therapeutic preparations may contain the compounds to be used according to the invention at a concentration of from 0.01 to 1.0% by weight, preferably from 0.05 to 0.1% by weight; for systemic application, the therapeutic preparations preferably contain a daily dose of up to 100 mg, in individual doses of from 1 to 5 mg.

Conventionally used pharmaceutical auxiliaries are, eg., alcohols, eg. isopropanol, oxyethylated castor oil or oxyethylated hydrogenated castor oil, polyacrylic acid, glycerol monostearate, liquid paraffin, polyethylene glycol 400, polyethylene glycol 400 stearate and ethoxylated fatty alcohols for local application, and lactose, propylene glycol and ethanol for systemic application.

EXAMPLE 1

11-cis-13-Desmethyl-vitamin-A-acid



192 g (1.5 moles) of fumaraldehyde-acid ethyl ester are added to a solution of 1.5 moles of β-ionylidene-ethyl-triphenylphosphonium chloride in dimethylformamide, the mixture is cooled to −20°C and 3 moles of sodium ethylate are added. After stirring for three hours at room temperature, the reaction mixture is poured into excess 20% strength sulfuric acid. The whole is extracted with five times 800 ml of n-heptane and the combined heptane extracts are washed with three times 1 l of 60% strength aqueous methanol, and once with 2 l of water. After drying and concentrating, 405 g of crude oil are obtained. The crude oil and 1.85 l of a 1N solution of potassium hydroxide in ethanol are heated for 2 hours under reflux. The mixture is acidified with 600 ml of 20% strength sulfuric acid and extracted with ether, the ether phase is washed with water and concentrated after drying. 362 g of crude product are obtained and are dissolved in 4 l of warm petroleum ether. On cooling to −20°C, 154 g of a crystalline mixture can be isolated; according to the 220 MHz NMR spectrum, this consists of all-trans-13-desmethyl-vitamin-A-acid and 11-cis-13-desmethyl-vitamin-A-acid.

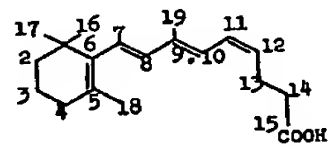
50 g of pure 11-cis-13-desmethyl-vitamin-A-acid can be isolated by repeated recrystallization from methanol.

Yellow crystals. Melting point: 151—156°C.

Analysis: $C_{19}H_{26}O_2$ Molecular weight=286.40

found:	C 79.5%	H 8.8%	O 11.2%
calculated:	C 79.68%	H 9.15%	O 11.17%

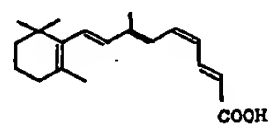
220 MHz-HNMR: 11-cis-13-desmethyl-vitamin-A-acid.
UV: λ max=354 nm
in isopropanol
E_1^1=1,200
13 C-NMR ($CDCl_3$ TMS standard)



The modified numbering shown in the above formula was only used for the purpose of attribution of the NMR spectrum, in accordance with O. Isler, Carotenoids, Basel, 1974.

Carbon atom	Chemical shift (ppm)
1	34.3
2	39.7
3	19.3
4	33.2
5	130.4
6	137.5
7	129.8
8	137.2
9	141.4
10	124.1
11	134.1
12	125.1
13	141.0
14	120.0
15	172.8
16	29.0
17	29.0
18	21.7
19	12.5

EXAMPLE 2
11-cis-13-Desmethyl-vitamin-A-acid



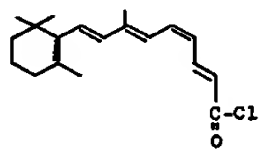
68 g (3.78 moles) of ammonia are passed into a solution of 0.652 mole of β-ionylidene-ethyl-triphenylphosphonium chloride and 66 g (0.66 mole) of fumaraldehyde-acid in 1,600 ml of methanol at from −20°C to −25°C. 100 ml of a 30% strength sodium methylate solution in methanol are added. The mixture is stirred for 1 1/2 hours at room temperature and then for 1/2 an hour at 40°C. It is concentrated on a rotary evaporator and the residue is acidified with 10% strength sulfuric acid and extracted with ether. The ether phase is washed with water, dried and concentrated. The residue is purified by column chromatography on silica gel (eluant: petroleum ether and a 10:1 petroleum ether:ether mixture) and is recrystallized from methanol.
Yield: 30.3%.

Analysis $C_{19}H_{26}O_2$ Molecular weight=286.40
found: C 79.5% H 9.0% O 11.6%
calculated: C 79.68% H 9.15% O 11.17%

UV: λ max=355 nm
in ethanol
E_1^1=1,180

EXAMPLE 3

11-cis-13-Desmethyl-vitamin-A-acid chloride

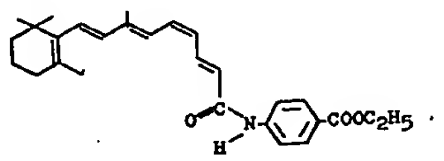


20 g (0.07 mole) of 11-cis-13-Desmethyl-vitamin-A-acid are dissolved in 300 ml of dry ether and 5.7 ml of dry pyridine. 5.5 ml of distilled thionyl chloride in 20 ml of dry ether are added dropwise in the course of 45 minutes at −10°C, under a blanket of nitrogen, and with exclusion of moisture. The mixture is stirred for a further 1/2 hour at −10°C and for 2 hours at room temperature, and the pyridine hydrochloride which has precipitated is filtered off. The solution of 11-cis-13-desmethyl-vitamin-A-acid chloride is immediately used for further reaction.

all-trans-13-Desmethyl-vitamin-A-acid chloride is prepared in the same way.

EXAMPLE 4

11-cis-13-Desmethyl-vitamin-A-acid anilide-4′-carboxylic acid ethyl ester



A freshly prepared solution of 0.035 mole of 11-cis-13-desmethyl-vitamin-A-acid chloride in 150 ml of dry ether is added to a suspension of 11.6 g (0.07 mole) of p-aminobenzoic acid ethyl ester in 50 ml of dry ether and the mixture is heated for 4 hours under reflux. After filtration, the ether filtrate is washed with water, dried and concentrated. The oil which remains is stirred with methanol and the product is then repeatedly recrystallized from methanol.

Yield: 39%.

Yellow crystals. Melting point: 107—112°C; the product is a single substance, according to thin layer chromatography.

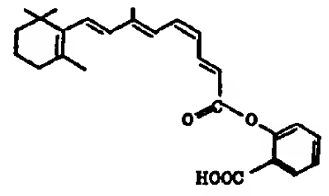
Analysis: Molecular weight=433.57

found:	C 77.0%	H 7.8%	N 3.7%	O 11.2%
calculated:	C 77.56%	H 8.14%	N 3.23%	O 11.07%

The 220 MHz H-NMR spectrum demonstrates the structure of 11-cis-13-desmethyl-vitamin-A-acid anilide-4′-carboxylic acid ethyl ester.

EXAMPLE 5

11-cis-13-Desmethyl-vitamin-A-acid salicylic acid ester



0.035 mole of pyridine is added to a freshly prepared solution of 10 g (0.035 mole) of 11-cis-13-desmethyl-vitamin-A-acid chloride in 150 ml of dry ether and a solution of 4.84 g (0.035 mole) of salicylic acid in 20 ml of dry ether is added dropwise. After stirring for 3 hours at room temperature, the mixture is filtered; the filtrate is washed with dilute hydrochloric acid and with water, dried and concentrated. The crude product is purified by column chromatography (silica gel, eluant petroleum ether+ether). It is recrystallized from a 10:1 mixture of petroleum ether: ether at −30°C.

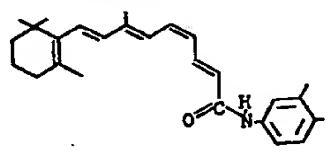
Yellow crystals. Melting point: 130—138°C.

Analysis:

found:	C 76.3%	H 7.6%	O 15.8%
calculated:	C 76.82%	H 7.44%	O 15.74%

UV: λ max=368 nm
in ethanol
E_1^1=836
The H-NMR spectrum and IR spectrum agree with the structure.

EXAMPLE 6
11-cis-13-Desmethyl-vitamin-A-acid 3',4'-dimethylaniline



A freshly prepared solution of 0.1 mole of 11-cis-13-desmethyl-vitamin-A-acid chloride is added to a solution of 24.2 g (0.2 mole) of 3,4-dimethylaniline in 100 ml of dry ether and the mixture is heated under reflux for 6 hours. It is then filtered and the ether filtrate is washed with dilute hydrochloric acid and with water, dried and concentrated. The oily crude product is recrystallized from cold petroleum ether and is further purified by recrystallization from aqueous ethanol.
Yellow crystals. Melting point: 156—161°C.

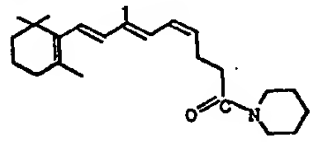
Analysis: $C_{27}H_{35}NO$. Molecular weight=389.56.

found:	C 83.2%	H 8.4%	N 4.0%	O 4.4%
calculated:	C 83.24%	H 9.06%	N 3.60%	O 4.11%

UV in ethanol
λ max=367 nm
E_1^1=1,236.

The H-NMR spectrum and IR spectrum agree with the structure.

EXAMPLE 7
11-cis-13-Desmethyl-vitamin-A-acid piperidide



A freshly prepared solution of 0.035 mole of 11-cis-13-desmethyl-vitamin-A-acid chloride in dry ether is added dropwise to a solution of 6.93 ml (0.07 mole) of piperidine in 100 ml of dry ether at room temperature. After stirring for 4 hours, the mixture is filtered and the filtrate is washed with dilute hydrochloric acid and with water, dried and concentrated. The crude product is recrystallized once from petroleum ether and twice from aqueous ethanol.
Yellow crystals. Melting point: 114—116°C.

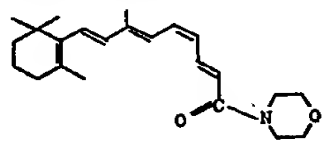
Analysis: $C_{24}H_{35}NO$. Molecular weight=1,258.

found:	C 81.8%	H 9.8%	O 4.7%	N 4.3%
calculated:	C 81.53%	H 9.98%	O 4.52%	N 3.96%

UV (ethanol)
λ max=356 nm
E_1^1=1,258

The H—NMR spectrum and IR spectrum agree with the structure.

EXAMPLE 8
11-cis-13-Desmethyl-vitamin-A-acid morpholide



This is prepared analogously to Example 4. After purification by column

chromatography on neutral aluminium oxide (eluant hexane : ether : methanol = 50 : 10 : 2), the product is recrystallized from petroleum ether.

Yellow crystals. Melting point: 90—93.5°C.

Analysis:

found:	C 76.90%	H 9.5%	O 9.5%	N 4.6%
calculated:	C 77.70%	H 9.35%	O 9.0%	N 3.94%

UV (ethanol)
max = 358 nm
$E_1^{1\%}$ = 1,132

The IR spectrum and H-NMR spectrum agree with the structure.

The compounds of the invention have been found to be pharmacologically-active and in particular to exhibit an activating effect on cell regeneration.

Suitable pharmaceutical preparations or medicament carriers for external application are exemplified in the Examples which follow:—

EXAMPLE 9

Solution

11-cis-13-Desmethyl-vitamin-A-acid		0.5 g
Oxyethylated hydrogenated castor oil (Cremophor RH 40 from BASF AG, Ludwigshafen—"Cremophor" is a Registered Trade Mark)		35.0 g
Polyethylene glycol 400		35.0 g
Oxyethylated castor oil (Softigen 767, from Chemische Werke Witten—"Softigen" is a Registered Trade Mark)		10.0 g
Demineralized water	ad	100.0 g

The Cremophor RH 40 and Softigen 767 are mixed and heated to 70°C. The active ingredient is dissolved whilst stirring and polyethylene glycol 400 is added. The solution is then cooled to 40°C and water heated to 40°C is added slowly whilst stirring. The final solution is filtered and filled into, e.g., 100 ml flasks.

EXAMPLE 10

Cream

11-cis-13-Desmethyl-vitamin-A-acid		1.0 g
Butylhydroxytoluene		0.1 g
Glycerol monostearate		11.0 g
Polyethylene glycol 400 stearate		6.0 g
Ethoxylated fatty alcohol		4.0 g
Liquid paraffin		10.0 g
p-Hydroxybenzoic acid esters (Nipasteril, from Nipalaboratorium Hamburg)		0.2 g
Perfume oil		0.1 g
Demineralized water	ad	100.0 g

The fats are melted and the very finely powdered active ingredient and the butylhydroxytoluene are distributed therein whilst stirring at 65°C (solution I). The water is boiled up with the Nipa ester and cooled to 65°C (solution II). Solution II is emulsified, a little at a time, in solution I, whilst stirring well. After cooling to 45°C, the perfume oil is added and the emulsion is cooled to room temperature whilst stirring. The final cream is filled into tubes with an internal protective lacquer.

EXAMPLE 11

Gel

11-cis-13-Desmethyl-vitamin-A-acid		0.01 g
Butylhydroxytoluene		0.1 g
Oxyethylated castor oil (Cremophor EL, from BASF AG, Ludwigshafen)		35.0 g
Isopropanol		20.0 g
Polyacrylic acid (Carbopol, from Goodrich Hamburg—"Carbopol" is a Registered Trade Mark)		1.5 g

Gel—(cont.)

Triethanolamine		0.002 g
p-Hydroxybenzoic acid esters (Nipasteril, from Nipalaboratorium Hamburg)		0.2 g
Demineralized water	ad	100.0 g

The Cremophor EL is heated to 60°C, the active ingredient and the butylhydroxytoluene are dissolved whilst stirring and the isopropanol, in which the Nipa esters have been dissolved, is admixed (solution I). The Carbopol is distributed in the water, with vigorous stirring (solution II). Solution II is admixed, a little at a time, to solution I, whilst stirring well. The pH of the mixture is brought to 4.5 with triethanolamine. The final gel is filled into tubes with an internal protective lacquer.

EXAMPLE 12

Solution

11-cis-13-Desmethyl-vitamin-A-acid salicylic acid ester		0.5 g
Oxyethylated hydrogenated castor oil (Cremophor RH 40, from BASF AG, Ludwigshafen)		35.0 g
Polyethylene glycol 400		35.0 g
Oxyethylated castor oil (Softigen 767, from Chemische Werke Witten)		10.0 g
Demineralized water	ad	100.0 g

The Cremophor RH 40 and Softigen 767 are mixed and heated to 70°C. The active ingredient is dissolved therein whilst stirring, and polyethylene glycol 400 is added. The solution is then cooled to 40°C and water heated to 40°C is added slowly whilst stirring. The final solution is filtered and filled into, eg., 100 ml flasks.

EXAMPLE 13

Cream

11-cis-13-Desmethyl-vitamin-A-acid salicylic acid ester		1.0 g
Butylhydroxytoluene		0.1 g
Glycerol monostearate		11.0 g
Polyethylene glycol 400 stearate		6.0 g
Ethoxylated fatty alcohol		4.0 g
Liquid paraffin		10.0 g
p-Hydroxybenzoic acid esters (Nipasteril, from Nipalaboratorium Hamburg)		0.2 g
Perfume oil		0.1 g
Demineralized water	ad	100.0 g

The fats are melted and the very finely powdered active ingredient and the butylhydroxytoluene are distributed therein whilst stirring at 65°C (solution I). The water is boiled up with the Nipa ester and cooled to 65°C (solution II). Solution II is emulsified, a little at a time, in solution I, whilst stirring well. After cooling to 45°C, the perfume oil is added and the emulsion is cooled to room temperature whilst stirring. The final cream is filled into tubes with an internal protective lacquer.

EXAMPLE 14

Gel

11 - cis - 13 - Desmethyl - vitamin - A - acid salicylic acid ester		0.01 g
Butylhydroxytoluene		0.1 g
Oxyethylated castor oil (Cremophor EL, from BASF AG, Ludwigshafen)		35.0 g
Isopropanol		20.0 g
Polyacrylic acid (Carbopol, from Goodrich Hamburg		1.5 g
Triethanolamine		0.002 g
p-Hydroxybenzoic acid esters (Nipasteril, from Nipalaboratorium Hamburg)		0.2 g
Demineralized water	ad	100.0 g

The Cremophor EL is heated to 60°C, the active ingredient and the isopropanol, in which the Nipa esters have been dissolved whilst stirring and the isopropanol, in which the Nipa esters have been dissolved, is admixed (solution I). The Carbopol is

distributed in the water, with vigorous stirring (solution II). Solution II is admixed, a little at a time, to solution I, whilst stirring well. The pH of the mixture is brought to 4.5 with triethanolamine. The final gel is filled into tubes with an internal protective lacquer.

EXAMPLE 15

Hair lotion

11-cis-13-Desmethyl-vitamin-A-acid		0.5 g
Ethanol		60.0 g
Fatty acid ester of a polyol		0.5 g
Lactic acid		0.12 g
Perfume		1.0 g
Demineralized water	ad	100.0 g

The active ingredient, the perfume and the fatty acid ester of a polyol are dissolved in ethanol and the water and the lactic acid are added. After 5 days' storage, the mixture is filtered and filled into brown bottles.

Examples of preparations or medicinal carriers particularly suitable for systemic application are:

EXAMPLE 16

Drops

11-cis-13-Desmethyl-vitamin-A-acid		0.1 g
Propylene glycol		25.0 g
Ethyl alcohol	ad	50.0 g

The ethyl alcohol and propylene glycol are mixed and the active ingredient is dissolved therein whilst heating at 35°C and stirring. After filtration, the solution is filled into dark-colored dropper bottles.

EXAMPLE 17

Hard gelatine capsules

11-cis-13-Desmethyl-vitamin-A-acid		0.005 g
Lactose	ad	0.25 g

The constituents are forced through a sieve, mixed and filled into size 2 hard gelatine capsules on a capsule filling and sealing machine.

EXAMPLE 18

Drops

11-cis-13-Desmethyl-vitamin-A-acid salicylic acid ester		0.1 g
Propylene glycol		25.0 g
Ethyl alcohol	ad	50.0 g

The ethyl alcohol and propylene glycol are mixed and the active ingredient is dissolved therein whilst heating at 35°C and stirring. After filtration, the solution is filled into dark-colored dropper bottles.

EXAMPLE 19

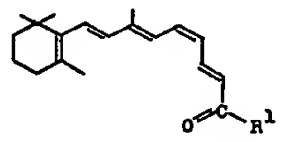
Hard gelatine capsules

11-cis-13-Desmethyl-vitamin-A-acid salicylic acid ester		0.005 g
Lactose	ad	0.25 g

The constituents are forced through a sieve, mixed and filled into size 2 hard gelatine capsules on a capsule filling and sealing machine.

WHAT WE CLAIM IS:—

1. A compound which is an 11-cis-13-desmethyl-vitamin-A-acid or a derivative thereof and which has the general formula:—



I

wherein R^1 is hydroxy, alkoxy of 1 to 4 carbon atoms, phenoxy optionally substituted with hydroxy or carboxyl, amino optionally mono- or di-substituted with alkyl of 1 to 4 carbon atoms or phenyl optionally substituted with hydroxyl, alkyl or 1 to 4

carbon atoms, carboxyl, carboxymethyl or carboxyethyl, a saturated 3- to 6-member heterocyclic ring containing a nitrogen heteroatom and optionally also an oxygen heteroatom, acyl of 2 to 4 carbon atoms, azido, hydrazino optionally substituted with methyl or phenyl, or a group of the formula: $C_{18}H_{25}CO—O—$ having the configuration of 11-cis-13-desmethyl-vitamin-A-acid.

2. 11-cis-13-desmethyl-vitamin-A-acid.

3. 11 - cis - 13 - desmethyl - vitamin - A - acid anilide - 4' - carboxylic acid ethyl ester.

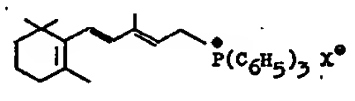
4. 11-cis-13-desmethyl-vitamin-A-acid salicylic acid ester.

5. 11-cis-13-desmethyl-vitamin-A-acid 3',4'-dimethylanilide.

6. 11-cis-13-desmethyl-vitamin-A-acid piperidide.

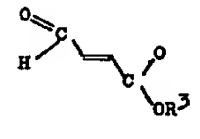
7. 11-cis-13-desmethyl-vitamin-A-acid morpholide.

8. A process for the manufacture of a compound as claimed in Claim 1, optionally in the form of an isomer mixture in which is also present the corresponding all-trans compound, which process comprises reacting a compound of the formula:—



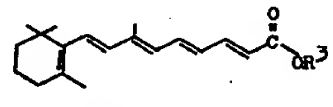
II

wherein $X^{\ominus}$ is an organic or inorganic acid radical, with a compound of the formula:—



III

wherein R^3 is hydrogen, alkyl of 1 to 4 carbon atoms, an ammonium ion or an alkali metal ion, the reaction being effected, at from −20 to +30°C, in an inert solvent and in the presence of a base, recovering the resulting isomer mixture of compounds of the formulae:—



IV

and thereafter effecting a step as specified below:—

(i) recovering the isomer mixture as product,

(ii) recovering from the isomer mixture referred to in (i) a cis-compound as product,

(iii) treating the isomer mixture referred to in (i) or the cis-compound recovered in step (ii) to effect conversion thereof to acid form when said isomer mixture or said cis-compound is in other than an acid or to effect conversion thereof to non-acid form when said isomer mixture or said cis-compound is in acid form,

(iv) treating an isomer mixture formed by conversion as specified in (iii) to recover therefrom a cis-compound,

(v) treating a cis-compound recovered in step (iv) to effect conversion thereof to an acid when said cis-compound is other than an acid or to effect conversion thereof to non-acid form when said cis-compound is an acid.

9. A process as claimed in Claim 8 and substantially as hereinbefore described in any one of Examples 1 to 4 and 6 to 10.

10. A compound as claimed in Claim 1 and whenever obtained by a process as claimed in Claim 8 or Claim 9.

11. A pharmaceutical preparation which contains one or more compounds as claimed in Claim 1 as an active ingredient, together with one or more conventional carriers and/or one or more conventional diluents.

12. A preparation as claimed in Claim 11 wherein the active ingredient is 11-cis-13-desmethyl-vitamin-A-acid or 11-cis-13-desmethyl-vitamin-A-acid salicyclic acid ester.

13. A preparation as claimed in Claim 11 and substantially as hereinbefore described in any one of the Examples.

14. An isomer mixture comprising an 11-cis-13-desmethyl-vitamin-A-acid or a derivative thereof together with an all-trans-13-desmethyl-vitamin-A-acid or a derivative thereof.

15. An isomer mixture as claimed in Claim 14 and obtained by a process as claimed in Claim 8 or Claim 9.

16. A pharmaceutical preparation which contains one or more compounds as claimed in Claim 1 as an active ingredient together with an all-trans-13-desmethyl-vitamin-A-acid or a derivative thereof as a further active ingredient, together with one or more conventional carriers and/or one or more conventional diluents.

J. Y. & G. W. JOHNSON,
Furnival House,
14—18, High Holborn,
London WC1V 6DE.
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Agents for the Applicants.

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